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Editorial

Current state of knowledge on the use of drug-coated balloon in coronary bifurcation lesions

Estado actual del conocimiento sobre el uso del balón farmacoactivo en las lesiones en bifurcación

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The use of drug-coated balloons (DCB) to treat stenotic coronary artery lesions is a treatment strategy whose main asset is to avoid leaving a permanent intracoronary stent device. Although highly effective in the percutaneous coronary intervention setting, it is associated with a risk of acute thrombosis, future events like restenosis, and late thrombosis following processes known as neointimal proliferation, neoatherosclerosis or fractures of material. This could be even more relevant in younger patients with a long trajectory of possible coronary events ahead of them.

The use of DCB is widely accepted to treat in-stent restenosis and de novo lesions in small vessels[1], and it is considered an interesting option in patients with high risk of bleeding. Another possible indication currently under scrutiny due to its possible potential is the management of bifurcations—one of the most interesting indications of all. However, clearly defined recommendations have not been established yet.[2]

Over the last few years, small clinical trials have been published on the use of DCB in this indication; although they have not proven definitive for a strong guideline recommendation, they provide valuable data. In general, trials have grouped into those looking into the safety and efficacy profile of DCB—without comparison group—and trials that compared strategies with DCBs or conventional balloons (CB).

PROSPECTIVE NON-RANDOMIZED TRIALS WITHOUT COMPARISON CONTROL GROUP

Table 1 shows 5 small trials (between 28 and 50 patients) including this type of different strategies with acceptable results regarding late lumen loss and safety.[3-9]

TRIALS COMPARING THE RESULTS TO DIFFERENT STRATEGIES AND 2 COMPARISON GROUPS, MOST OF THEM RANDOMIZED

Table 2 shows the 6 landmark trials comparing different strategies, 5 of them randomized,[10-14] and 1 non-randomized.[15]

CONCLUSIONS FROM TRIAL RESULTS

1. The use of bare metal stents (now in disuse) neutralizes all positive effects from the DCB in the main or side branch (DEBIUT[11] and BABILON trials.[12])

2. In lesions without proximal damage to the bifurcation, an early strategy of DCB can only be considered in 1 or in both branches (PEPCAD-BIF.[10]) Also, non-flow-limiting dissections have good prognosis at follow-up.

3. The use of DCB alone into the main branch can also have positive effects on the side branch ostium. Even using a limus-eluting stent in the main branch can only have a positive remodeling effect on the side branch ostium (aside from the study conducted by Her et al.,[9] the BABILON trial already suggested it.[12]). In any case, the use of a DCB as a single stentless strategy (unless results are poor or in the presence of flow-limiting dissections) seems like a reasonable option with a favorable long-term remodeling both in the main and side branches.

4. The use of a limus-eluting stent in the main branch with a DCB implanted in the side branch (currently the most widely used strategy) can improve angiographic intraluminal parameters like late lumen loss or minimum lumen diameter without any significant clinical repercussions on the long-term events (the BEYOND trial.[14]). This is probably so because, in the other group, late lumen loss in the side branch is also small since events are more conditioned by the main compared to the side branch (BABILON[12]), and also because there are barely any myocardial infarctions or target lesion revascularizations associated with the side branch in any of the 2 groups.

5. The results obtained with different balloons could also be different.

However, we should mention other aspects like vessel length, and not only vessel diameter since some studies demonstrate that length—and not diameter—can be a more important predictor of the impact side branch occlusion. Moreover, almost all these trials

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Table 1. Non-randomized, prospective clinical trials without comparison control group

Trial	Name or author and DCB	No. of patients	LLL TLR events, and restenosis	Restenosis, and MACE
DCB into both branches and BMS into the main branch	PEPCAD-V[4] (Sequent Please B. Braun, Germany)	28	0.21 ± 0.48 in the SB 0.38 ± 0.46 mm in the MB Only 1 TLR (3.57%) and 3 restenoses (10.7%)	2 patients (7.14%) had late thrombosis at 6 and 8 months
Paclitaxel DES into the MB, and DCB into the SB	DEBSIDE (NCT01485081) (Danubio, France)	50	LLL in the SB: -0.04 ± 0.34 mm and in the MB: 0.54 ± 0.60 mm TLR in 1 patient (2%) Restenosis, 7.5.	1 AMI (2%) without cardiac deaths
-limus DES into the MB, and DCB into the SB	BIOLUX-A (www.anzctr.org.au, ID 335843) (Pantera Lux, Biotronik AG, SwitzeSBand)	35	LLL in the SB: 0.1 ± 0.43 mm 1 TLR (2.85%) No restenosis	1 patient died, and 3 AMIs were reported in different vessels
	SARPEDON[5] (Pantera Lux, BIOTRONIK AG, Bülach, Switzerland)	50	TLR, 5.2% at 1 year 4% of restenosis in the MB, and 6% in the SB	Stent thrombosis, 0%
	Estudio de Valencia et al.[6] (Sequent Please)	54	TLR, 3.6%	Overall mortality, 3.7%
DCB alone into both branches	Schulz et al.[7] (Sequent Please)	39	10% restenosis, and all in the left main coronary artery bifurcation	
	Bruch et al.[8] (Sequent Please)	127	TLR, 4.5	MACE, 6.1% Use of bailout stent in 45%
DCB alone into 1 branch	Her et al.[9] (Sequent Please) (Only in the MB)	16	There was a significant increase in the SB luminal area at 9 months, 0.37 mm^2 ± 0.64 mm^2; ($P = .013$), with a similar increase in the MB luminal area	The use of DCB alone in the MB also had a favorable impact on an area gain of 52% in the SB ostium
	Vaquerizo et al. (NCT01375465) (Eurocor GmbH, Germany) (Only in the SB and 001 lesions)	31	LLL in the SB, 0.32 mm^2 ± 0.73 mm^2, and binary restenosis, and TLR of 22.5%	High need for bailout BMS (14%) 1 AMI (3.2%)

AMI, acute myocardial infarction; BMS, bare metal stent; CB, conventional balloon; DCB, drug-coated balloon; DES, drug-eluting stent; LLL, late lumen loss; MACE, major adverse cardiovascular events; MB, main branch; SB, side branch; TLR, target lesion revascularization.

included side branch lesions < 10 mm in length, which is a well-known favorable predictor for the provisional stenting technique. Side branch lesions > 10 mm plus other signs of complexity like calcium, etc. can require the double stenting strategy, especially in left main coronary artery bifurcation lesions.[16]

Its role in more complex settings like left main coronary artery bifurcations or in-stent restenosis in bifurcations has also been studied, with reasonably good results.[17,18]

The article by Valencia et al.[6] recently published in *REC: Interventional Cardiology* falls within the category of observational studies without control group that do not include angiographic measurements to allow, at least, a rough result comparison with other studies. This article combines treatment strategies like drug-eluting stent implantation into the main vessel in 71% of the cases or DCB alone into the main branch in 29% of the cases followed by DCB implantation into the side branch or DCB alone into the side branch, since 18% of the lesions were Medina 0,0,1 while, overall, 37.5% had no proximal damage.

According to the authors, this article contribution is the presentation of the clinical results of a small series of 54 patients with 55 lesions and the authors' management of this type of lesions without excluding patients with higher risk of restenosis, as 32.1% of the patients with in-stent restenosis in the bifurcation and 8.9% with left main coronary artery lesions showed. Nevertheless the clinical outcomes are good with a median follow-up of 12 months. The rates of all-cause mortality, lesion thrombosis or infarction, and target lesion revascularization were 3.7%, 0%, and 3.6%, respectively, precisely in the most unfavorable cases of all, patients with in-stent restenosis.

The study limitations are obvious and well-established by the authors in the corresponding section. In brief, a small number of patients, no control group or angiographic follow-up, and the assumption that asymptomatic patients had no side branch restenosis. Also, since follow-up was not conducted on-site, possible developments of new Q waves associated with the side branch segment could not be detected. However, the study shows what many interventional cardiologists currently do in their cath labs and maintains interest for this strategy that should undoubtedly be taken into consideration when treating bifurcations. The most recent trials on drug-eluting stent and DCB implantation into the main and side branch, respectively, show good results in both branches, though with small differences in the repercussion of clinical events. Randomized clinical trials with a large cohort of patients are needed so that all possible trends favorable to the side branch become significant. Despite the presence of complex patients, the results from the trial conducted by Valencia et al.[6] are good, promising, and their data welcome.

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None whatsoever.

Table 2. Trials that compared the results with different strategies in 2 randomized comparison groups (except for the one conducted by Li et al.[15])

Trial	Name and no. of patients	LLL	Restenosis and MACE, TLR events	Takeaway
DCB alone vs CB as a first-line therapy in lesions without damage to the proximal segment	PEPCAD-BIF[10] (Sequent Please) 64 patients	LLL in the DCB group, 0.08 mm ± 0.31 mm vs 0.47 ± 0.61 mm in the CB group (P = .006).	Rates of restenosis of 26% vs 6% Rates of TLR of 9% vs 3% Favorable to DCB	In this type of lesions, stents were required in < 10% of the cases only
DCB vs CB in the SB with the use of BMS in the MB	DEBIUT[11] (Dior-I, Eurocor GmbH, Germany) 117 patients A) DCB in both branches and BMS in the MB B) BMS in the MB, and CB in the SB C) Paclitaxel DES in the MB, and CB in the SB	LLL in the SB was 0.19 mm ± 0.66 mm in group A, 0.21 mm ± 0.57 mm in group B, and 0.11 mm ± 0.43 mm in group C (P = .001) LLL in the MB, 0.31 mm ± 0.48 mm in group A vs 0.16 mm ± 0.38 mm in group B (P = .15)	The rates of binary restenosis were 24.2%, 28,6%, and 15%; (P = .45), and the rates of MACE were 20%, 29.7%, and 17.5%; (P = .40) in groups A, B, and C, respectively	With this strategy, pretreatment of both branches with DCB was not superior to conventional BMS with the provisional stenting technique. Also, the use of DES was superior to DCB plus BMS
	BABILON[12] (Sequent Please) 108 patients A) DCB in both branches, and BMS in the MB B) Everolimus DES in the MB, and CB in the SB	LLL in the SB, –0.04 mm ± 0.76 mm in group A vs -0.03 mm ± 0.51 mm in group B (P = .983)	The rates of MACE and TLR were higher in group A in the MB (17.3% vs 7.1% [P = .10], and 15.4% vs 3.6%; [P = .045]) due to more restenosis in the MB (13.5% vs 1.8%; P = .027)	Bifurcation pretreatment with DCB with BMS in the MB had more LLL and higher rates of MACE vs DES in the MB and CB in the SB Also, both strategies gave similar and very good results in the SB
Paclitaxel DES in the MB with CB vs DCB in the SB	Herrador et al.[13] (Sequent Please) 50 patients	LLL, 0.40 mm ± 0.50 mm vs 0.09 mm ± 0.40 mm, (P = .01) favorable to the DCB group	The rates of SB restenosis were 20% vs 7%, (P = .08), and the rates of TLR, 22% vs 12% (P = .16)	The rates of MACE at 12 months were 24% vs 11% (P = .11)
-limus DES in the MB with CB vs DCB in the SB	BEYOND[14], (Bingo, Yinyi Biotech, China) 222 patients with coronary bifurcation lesions excluding the left main coronary artery	Significantly lower LLL in the DCB compared to the CB group (–0.06 mm ± 0.32 mm vs 0.18 mm ± 0.34 mm; P < .0001)	The rates of restenosis were 28.7% vs 40% (P < .0001)	No differences regarding MACE (0.9% vs 3.7%, P = .16) or non-fatal AMI were found (0% vs 0.9%, P = .49)
	Li et al.[15] (Sequent Please) NON-randomized	LLL of SB in the DCB group was lower compared to the CB group (0.11 mm ± 0.18 mm vs 0.19 mm ± 0.25 mm; P = .024) at 12-month follow-up	Multivariate COX analysis indicated that the DCB group had less MACE (23.9% vs 12.8%; P = .03)	Better results in the SB with DCB and fewer composite endpoints, but basically at the expense of unstable angina

AMI, acute myocardial infarction; BMS, bare metal stent; CB, conventional balloon; DCB, drug-coated balloon; DES, drug-eluting stent; LLL, late lumen loss; MACE, major adverse cardiovascular events; MB, main branch; SB, side branch; TLR, target lesion revascularization.

CONFLICTS OF INTEREST

None reported.

REFERENCES

1. Jeger RV, Eccleshall S, Wan Ahmad WA, et al. Drug-Coated Balloons for Coronary Artery Disease: Third Report of the International DCB Consensus Group. *JACC Cardiovasc Interv.* 2020;13:1391-1402.
2. Hildick-Smith D, Arunothayaraj S, Stankovic G, Chen SL. Percutaneous coronary intervention of bifurcation lesions. *EuroIntervention.* 2022;18: e273-e291.
3. Corballis NH, Paddock S, Gunawardena T, Merinopoulos I, Vassiliou VS, Eccleshall SC. Drug coated balloons for coronary artery bifurcation lesions: A systematic review and focused meta-analysis. *PLoS One.* 2021;16: e0251986.
4. Mathey DG, Wendig I, Boxberger M, Bonaventura K, Kleber FX. Treatment of bifurcation lesions with a drug-eluting balloon: the PEPCAD V (Paclitaxel Eluting PTCA Balloon in Coronary Artery Disease) trial. *EuroIntervention.* 2011;7 Suppl K:K61-65.
5. Jim MH, Lee MK, Fung RC, Chan AK, Chan KT, Yiu KH. Six month angiographic result of supplementary paclitaxel-eluting balloon deployment to treat side branch ostium narrowing (SARPEDON). *Int J Cardiol.* 2015;187: 594-597.
6. Valencia J, Torres-Mezcua F, Herrero-Brocal M, et al. Efectividad a largo plazo del balón farmacoactivo en el tratamiento de la rama lateral de lesiones en bifurcación. *REC Interv Cardiol.* 2022. https://doi.org/10.24875/RECIC.M22000317.
7. Schulz A, Hauschild T, Kleber FX. Treatment of coronary de novo bifurcation lesions with DCB only strategy. *Clin Res Cardiol.* 2014;103: 451-456.
8. Bruch L, Zadura M, Waliszewski M, et al. Results From the International Drug Coated Balloon Registry for the Treatment of Bifurcations. Can a Bifurcation Be Treated Without Stents? *J Interv Cardiol.* 2016;29(4): 348-356.
9. Her AY, Ann SH, Singh GB, et al. Serial Morphological Changes of Side-Branch Ostium after Paclitaxel-Coated Balloon Treatment of De Novo Coronary Lesions of Main Vessels. *Yonsei Med J.* 2016;57:606-613.

10. Kleber FX, Rittger H, Ludwig J, et al. Drug eluting balloons as stand alone procedure for coronary bifurcational lesions: results of the randomized multicenter PEPCAD-BIF trial. *Clin Res Cardiol*. 2016;105:613-621.
11. Stella PR, Belkacemi A, Dubois C, et al. A multicenter randomized comparison of drug-eluting balloon plus bare-metal stent versus bare-metal stent versus drug-eluting stent in bifurcation lesions treated with a single-stenting technique: six-month angiographic and 12-month clinical results of the drug eluting balloon in bifurcations trial. *Catheter Cardiovasc Interv*. 2012;80: 1138-1146.
12. López Mínguez JR, Nogales Asensio JM, Doncel Vecino LJ, et al. A prospective randomised study of the paclitaxel-coated balloon catheter in bifurcated coronary lesions (BABILON trial): 24-month clinical and angiographic results. *EuroIntervention*. 2014;10:50-57.
13. Herrador JA, Fernandez JC, Guzman M, Aragon V. Drug-eluting vs. conventional balloon for side branch dilation in coronary bifurcations treated by provisional T stenting. *J Interv Cardiol.* 2013;26:454-462.
14. Jing QM, Zhao X, Han YL, et al. A drug-eluting Balloon for the trEatment of coronarY bifurcation lesions in the side branch: a prospective multicenter ranDomized (BEYOND) clinical trial in China. *Chin Med J*. 2020;133:899-908.
15. Li Y, Mao Q, Liu H, Zhou D, Zhao J. Effect of Paclitaxel-Coated Balloon Angioplasty on Side Branch Lesion and Cardiovascular Outcomes in Patients with De Novo True Coronary Bifurcation Lesions Undergoing Percutaneous Coronary Intervention. *Cardiovasc Drugs Ther*. 2021;36: 859-866.
16. Zhang JJ, Ye F, Xu K, et al. Multicentre, randomized comparison of two-stent and provisional stenting techniques in patients with complex coronary bifurcation lesions: the DEFINITION II trial. *Eur Heart J*. 2020;41:2523-2536.
17. Liu H, Tao H, Han X, et al. Improved Outcomes of Combined Main Branch Stenting and Side Branch Drug-Coated Balloon versus Two-Stent Strategy in Patients with Left Main Bifurcation Lesions. *J Interv Cardiol*. 2022. https://doi.org/10.1155/2022/8250057.
18. Harada Y, Colleran R, Pinieck S, et al. Angiographic and clinical outcomes of patients treated with drug-coated balloon angioplasty for in-stent restenosis after coronary bifurcation stenting with a two stent technique. *EuroIntervention*. 2017;12:2132-2139.